The Examiner has withdrawn the restriction requirement. The following discussions address the obviousness rejections against claims 57-101 raised in the Office Action mailed October 1, 1997. The rejections against claims 24-42, 48-51 and 54-56 set forth in the Office Action mailed July 10, 1996 have been traversed by applicant in a response filed December 10, 1996, a copy of which is attached hereto.

Claims 24-38 and 54 are drawn to compositions and kits for amplifying a target nucleic acid sequence. The compositions and kits contain, among other things, an amplification primer or promoter-primer which has at least two members of the same nucleotide sequence but different 3' ends. The 3' end of one member is blocked to reduce or block extension by a polymerase and the 3' end of the other member is either unmodified or differently modified.

Claim 39 is directed to a kit for amplifying *Mycobacterial* nucleic acid containing a primer or promoter-primer targeting a specific region of 16S rRNA/rDNA (SEQ ID No: 1 or 2). Claim 100 is directed to a kit for amplifying *Mycobacterial* nucleic acid containing a primer or promoter-primer targeting a specific region of 23S rRNA/rDNA (SEQ ID No: 6 or 7).

Claims 40, 50 and 51 are directed to primers and promoter-primers targeting specific 16S rRNA/rDNA or 23S rRNA/rDNA regions of *Mycobacterium tuberculosis* (SEQ ID Nos: 1, 2, 6 and 7).

Claims 41, 48 and 49 are directed to kits for amplifying and detecting *Mycobacterial* nucleic acid targeting the 16S rRNA/rDNA region. The kits contain a primer or

promoter-primer targeting a specific region of 16S rRNA/rDNA (SEQ ID: 1 or 2) and a hybridization oligonucleotide targeting a specific region of 16S rRNA/rDNA (SEQ ID: 3).

Claims 42, 55 and 56 are directed to kits for amplifying and detecting *Mycobacterial* nucleic acid targeting the 23S rRNA/rDNA region. The kits contain a primer or promoter-primer targeting a specific region of 23S rRNA/rDNA (SEQ ID: 6 or 7) and a hybridization oligonucleotide targeting a specific region of 23S rRNA/rDNA (SEQ ID: 8).

Claims 57-66 are directed to nucleic acid hybridization probes targeting a specific 16S rRNA/rDNA (SEQ ID NO: 3) or 23S rRNA/rDNA region (SEQ ID NO: 8) of *Mycobacterium tuberculosis,* and specifically detectable nucleic acid hybrids formed between such probes and their targets.

Claims 67-73 are directed to amplification oligonucleotides targeting specific 16S rRNA/rDNA or 23S rRNA/rDNA regions of *Mycobacterium tuberculosis* (SEQ ID NOs: 2, 7, 22 and 23).

Claims 74-83 are directed to compositions for amplifying and detecting a specific 23S rRNA/rDNA region of *Mycobacterium tuberculosis* (SEQ ID NOs: 23, 8, 7, 9 and 10).

Claims 84-93 are directed to compositions for amplifying and detecting a specific 16rRNA/rDNA region of *Mycobacterium tuberculosis* (SEQ ID NOs: 22, 3, 2, 4 and 5).

Claims 94, 96 and 97 are directed to helper probes targeting specific 23S rRNA/rDNA regions of *Mycobacterium tuberculosis* and probe mixes comprising such a helper

probe and a nucleic acid hybridization probe targeting the same 23S rRNA/rDNA region of *Mycobacterium tuberculosis* (SEQ ID NOs: 9 and 10).

Claims 95, 98 and 99 are directed to helper probes targeting specific 16S rRNA/rDNA regions of *Mycobacterium tuberculosis* and probe mixes comprising such a helper probe and a nucleic acid hybridization probe targeting the same 16S rRNA/rDNA region of *Mycobacterium tuberculosis* (SEQ ID NOs: 4 and 5).

Claim 101 is directed to a composition useful for detecting *Mycobacterium tuberculosi.* This composition contains either (a) a nucleic acid hybridization assay probe targeting a specific 16S rRNA/rDNA or 23S rRNA/DNA region, (b) an amplification oligonucleotide targeting a specific 16S rRNA/rDNA or 23S rRNA/DNA region, (c) a kit containing the amplification oligonucleotide, or (d) a specifically detectable nucleic acid hybrid formed between the nucleic acid hybridization assay probe and its target nucleic acid.

A table which shows the relationship between the SEQ ID NOs and hybridization probes, amplification primers, and helper oligonucleotides is provided as Appendix A for the Examiner's reference.

I. THE SECTION 103 REJECTIONS

A. Claims 57-70, 74-77, 79-87, 89-93 and 101 are rejected under 35 U.S.C. § 103 over Rogall or Normand

The examiner rejected claims 57-70, 74-77, 79-87, 89-93 and 101 under 35 U.S.C. § 103 over Rogall or Normand. This rejection is respectfully traversed.

Rogall is only concerned with **16S** rRNA genes of *Mycobacterium* species and does not disclose any sequence from **23S** rRNA genes of *Mycobacterium* species. As illustrated by **Appendix A**, SEQ ID Nos: 6, 7, 8, 9, 10, 19 and 23 are derived from **23S** rRNA/rDNA of *Mycobacterium tuberculosis*. In that regard, claims 42, 55, 56, 74-83, 94, 96, 97 and 100 are directed to **23S** rRNA/rDNA of *Mycobacterium tuberculosis* and Rogall is not relevant prior art to these claims.

Rogall used PCR primers to synthesize "an approximately 1 kb gene fragment containing the 5' part of the gene coding for 16S rRNA" of *Mycobacterium* species. Rogall then sequenced the PCR products and aligned nucleotides 123-276 from different species in Figure 3 for comparison. The three PCR primers used by Rogall (pA, nucleotides 8-21; pE*, nucleotides 928-908; and pI*, nucleotides 1047-1027) and the four sequencing primers used by Rogall (pB, nucleotides 50-70; pC*, nucleotides 361-341; pC, nucleotides 341-361; and pD*, nucleotides 536-518) bind to 16S rRNA gene in regions that are different from the targets of SEQ ID Nos. 1, 2, 3, 4, 5, and 22.

In addition, because Rogall took the approach of sequence comparison for distinguishing different species of *Mycobacterium*, it did not describe or suggest the approach of detecting *Mycobacterium tuberculosis* by nucleic acid hybridization, let alone selecting primers or probes of about 10-100 nucleotides in length containing nucleotides 147-177 corresponding to SEQ ID NO: 2, nucleotides 200-229 corresponding to SEQ ID NO: 3, or nucleotides 257-276 overlapping with SEQ ID NO: 22.

The proper selection of hybridization locations for probes and primers targeting *Mycobacterium tuberculosis* is important in the claimed invention because rRNA in physiological samples frequently folds and forms secondary and tertiary structures which interfere with the hybridization of a complementary oligonucleotide with a region inside the folded structures.

The amplification primers and hybridization probes of the claimed invention are of specific length and are directed to specific regions of *Mycobacterium* rRNA/rDNA. In comparison with claim 101 or claim 57 and its dependent claims 58-66, Rogall would not have suggested to one skilled in the art to prepare an oligonucleotide of about 10 to about 100 nucleotides comprising SEQ ID NO: 3 for detecting *Mycobacterium tuberculosis* nucleic acid or for any other purposes.

In comparison with claim 101 or claim 67 and its dependent claims 68-73, Rogall would not have suggested to one skilled in the art an oligonucleotide of about 10 to about 100

nucleotides comprising SEQ ID NO: 2, 7, 22 or 23 for amplifying *Mycobacterium* nucleic acid or for any other purposes.

In comparison with claims 74-83, Rogall would not have suggested to one skilled in the art an oligonucleotide directed to **23S** rRNA/rDNA of *Mycobacterium tuberculosis*.

In comparison with claim 84 and its dependent claims 85-93, Rogall would not have suggested to one skilled in the art a composition containing a nucleic acid hybridization assay probe and an oligonucleotide of about 10 to about 100 nucleotides comprising SEQ ID NO: 22, 3, 2, 4, 5, or their complementary sequences.

Normand presents an even weaker case than Rogall against the claimed invention because Normand does not discuss *Mycobacteria* at all, but is concerned with the nucleotide sequence of an rRNA operon of actinomycete *Frankia*. This rRNA operon has 6481 nucleotides. Nucleotides 2712-2728 have the following sequence: GC**CGGAACAG GCTAAACC,** which contains 10 contiguous nucleotides from the 24 nucleotides of SEQ ID NO: 7, i.e., CGCGGAACAG GCTAAACCGC ACGC. Nothing in Normand suggests preparing oligonucleotides containing the complete sequence of SEQ ID NO: 7.

For the above stated reasons, Applicant respectfully submits that the rejections of claims 57-70, 74-77, 79-87, 89-93 and 101 based on Rogall and Normand be withdrawn.

B. Claims 71-73, 78 and 88 are rejected under 35 U.S.C. § 103 over Rogall, and further in view of Guatelli in view of Schuster

The examiner rejected claims 71-73, 78 and 88 under 35 U.S.C. § 103 over Rogall and further in view of Guatelli in view of Schuster. This rejection is respectfully traversed.

First of all, the composition of claim 78 is directed to 23S rRNA of *Mycobacterium tuberculosis*. None of Rogall, Guatelli and Schuster describes or suggests a primer or promoter-primer targeting the 23S rRNA of *Mycobacterium tuberculosis*, let alone the specific regions identifed in the claimed invention.

Claims 71-73 are dependent on claim 67. As discussed above, Rogall would not have suggested to one skilled in the art an oligonucleotide of about 10 to about 100 nucleotides comprising SEQ ID NO: 2, 7, 22 or 23 for amplifying *Mycobacterium* nucleic acid or for any other purposes. Neither would Guatelli or Schuster have suggested to one skilled in the art such an oligonucleotide because Guatelli is directed to a three-enzyme isothermal amplification method and Schuster describes an amplification method employing primers modified at their 3' ends.

Claim 88 is dependent on claim 84. As discussed above, Rogall would not have suggested to one skilled in the art a composition containing a nucleic acid hybridization assay probe and an oligonucleotide of about 10 to about 100 nucleotides comprising SEQ ID NO: 22, 3, 2, 4, 5, or their complementary sequences. Neither would Guatelli or Schuster.

For the above stated reasons, Applicant respectfully submits that the rejections of claims 71-73, 78 and 88 based on Rogall, Guatelli, and Schuster be withdrawn.

C. Claims 94-100 are rejected under 35 U.S.C. § 103 over Rogall in view of Hogan

The Examiner relied on Rogall for this rejection because Rogall "teaches a nucleic acid sequence which includes the sequence set forth in SEQ ID NO. 2." However, the helper probe of claims 94, 95, 97 and 99 consists essentially of the nucleotide sequence of SEQ ID NO: 4, 5, 9 or 10, none of which corresponds to the sequence set forth in SEQ ID NO: 2.

The probe mix of claim 96 contains a hybridization probe targeting a specific **23S** rRNA/rDNA region of *Mycobacterium tuberculosis*, which, as discussed above, is not disclosed by Rogall. The kit of claim 100 contains two primers/promoter-primers, one containing SEQ ID NO: 6 and the other containing SEQ ID NO: 7, none of which is described by Rogall.

In addition, as discussed above, Rogall would not have suggested to one skilled in the art to prepare a hybridization probe from about 10 to 100 nucleotides in length targeting SEQ ID NO. 3 or its fully complementary sequence of the same length.

For the above stated reasons, Applicant respectfully submits that the rejections of claims 94-100 based on Rogall and Hogan be withdrawn.

Accordingly, the claims are now in condition for allowance and a notice to that effect is respectfully requested. If the fee submitted in connection with this response is incorrect, please charge or credit Deposit Account No. 12-2475 for the appropriate amount.

Respectfully submitted,

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